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EXAMINER	
LEE, JAE W	

ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,795	SINCLAIR ET AL.	
	Examiner	Art Unit	
	JAE W. LEE	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5 and 7-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 5 and 7-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application status

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 06/09/2009 has been entered.

In response to the previous Office action, a final rejection (mailed on 12/08/2008), Applicants filed a response and amendment received on 06/09/2009. Said amendment canceled Claims 2-4, 6, 28 and 34, and amended Claims 1, 5, 7, 8, 11-15, 18, 24, 25, 27, 29, 30, 31 and 33. Thus, Claims 1, 5 and 7-25 are at issue and present for examination.

Applicants' arguments filed on 06/09/2009, have been fully considered, and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

It is noted by the Examiner that Claims 26, 27, 29-33 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b) as being drawn to a non-elected

invention as noted in the previous Office actions, a non-Final rejection (mailed on 3/31/08).

Claim Objections

The previous objection of Claim 1 for the recitation of "protein protomers which each comprise" is withdrawn by virtue of Applicants' amendment.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The previous rejection of Claim 1, 5 and 7-25 under 35 U.S.C. § 112, second paragraph for the recitation of the phrase, "a set of rotational symmetry axes extending in three dimensions" is withdrawn by virtue of Applicants' amendment.

The previous rejection of Claim 1, 5 and 7-25 under 35 U.S.C. § 112, second paragraph for the recitation of the words "first" and/or "further" in many different phrases, is withdrawn by virtue of Applicants' amendment.

The previous rejection of Claim 1, 5 and 7-25 under 35 U.S.C. § 112, second paragraph for the recitation of the phrase, "A protein lattice having … [1] the repeating unit comprising *protein protomers* …, [2] wherein the repeating unit comprises *protomers comprising at least a first monomer which is a monomer of a first oligomer*

assembly which has a set of rotational symmetry axes extending in three dimensions; and at least a further monomer fused to said first monomer which further monomer is a monomer of a further oligomer assembly, each further oligomer assembly having a rotational symmetry axis of the same order as one of the set of rotational symmetry axes of the first oligomer assembly and being aligned with the one of the set of rotational symmetry axes of the first oligomer assembly" is withdrawn by virtue of Applicants' amendment.

Claims 8 and 16-21 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 recites the phrase, "wherein the linking group is oriented relative to the first and second monomers in the protomer in its normal form prior to assembly to reduce any difference in the assembled lattice in either or both of the position and orientation of (a) the termini of said first monomers in their arrangement in said first oligomer assembly in its natural form symmetrically around one of said at least three rotational symmetry axes of said first oligomer assembly, and (b) the termini of said second monomers in their arrangement in said second oligomer assembly in its natural form symmetrically around said rotational symmetry axis of said second oligomer assembly" which is unclear and indefinite. It is unclear what the 'relative orientation of the linking group respect to the first and second monomer prior to assembly' must be in order to reduce any difference in the assembled lattice. Further, it is unclear what "the

position and orientation of (a) the termini of said first monomers in their arrangement in said first oligomer assembly in its natural form *symmetrically around one of said at least three rotational symmetry axes of said first oligomer assembly*, and (b) the termini of said second monomers in their arrangement in said second oligomer assembly in its natural form *symmetrically around said rotational symmetry axis of said second oligomer assembly*" mean (added emphasis). Overall, this claim is incomprehensible. The Examiner suggests Applicants to clarify the meaning of the noted phrase. In the interest of advancing prosecution, the noted phrase is not given any patentable weight.

Claim 16 and claims 17-21 dependent therefrom, recites the phrase, "the protomers are heterologous with respect to the monomers" which is unclear and indefinite. It is unclear how the protomers which comprise the monomers can be heterologous from the monomers. In the interest of advancing prosecution, the noted phrase is not given any patentable weight.

Claim 17 and claims 18-21 dependent therefrom, recites the phrase, "wherein the repeating unit includes protein protomers of two types, and wherein the two types of protomers include different monomers of the same heterologous oligomer assembly" which is unclear and indefinite. It is unclear what the second type of protomers are since the claim only list first of the two types, i.e., different monomers of the same heterologous oligomer assembly. Further, it is unclear what "different monomers of the same heterologous oligomer assembly" mean. In the interest of advancing prosecution, the noted phrase is not given any patentable weight.

Claim 18 and claims 19-21 dependent therefrom, recites the phrase, "are one of said different monomers of the same heterologous oligomer assembly, said heterologous oligomer assembly" which is unclear and indefinite. It is unclear what the noted phrase mean. In the interest of advancing prosecution, the noted phrase is not given any patentable weight.

Claim 20 recites the phrase "said heterologous oligomer assembly" which is unclear and indefinite. It is unclear what "said heterologous oligomer assembly" is referring to since it is unclear what it encompasses (see above rejections of claims 16-18 under 112 2nd paragraph). In the interest of advancing prosecution, the noted phrase is not given any patentable weight.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5 and 7-25 are rejected under 35 U.S.C. § 112, first paragraph, written description, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection was stated in the previous office action as it applied to previous claims 1, 5 and 7-25. In response to this rejection, Applicants have canceled Claims 2-

4, 6, 28 and 34, and amended Claims 1, 5, 7, 8, 11-15, 18, 24, 25, 27, 29, 30, 31 and 33, and traverse the rejection as it applies to the newly amended claims.

Applicants argue that Applicants are entitled to the genus claim directed to a protein lattice having a regular structure comprising a repeating unit of protein protomer(s) because Applicants had possession of the genus as evidenced by the present Specification. The Specification provides sufficient guidance for the structural and functional features common to the members of the genus and exemplifies a representative number of the genus. In addition to the remarks made in the previous Amendment filed on July 21, 2008, Applicants point out that the Specification exemplifies a sufficient number of species and adequate amount of teachings to satisfy the written description requirement. Figure 1 of the Specification depicts an example of a protein lattice established from assembly of a protomer represented by p4d4. The first oligomer assembly, as exemplified in Figure 1, is human ferritin heavy chain (HFH) which belongs to an octahedral P4 point group of order 4. The second oligomer assembly, as exemplified in Figure 1, is E. coli PurE which belongs to a dihedral D4 point group of order 4. The Specification also provides, in Figure 2, another protein lattice made from two mixed types of protomers. The first promoter of the protein lattice of Figure 2 comprises a first monomer of a first homologous oligomer assembly, namely E. coli dps, which belongs to a tetrahedral point group. The first monomer of the first protomer in Figure 2 is then fused to a second monomer of the first protomer, which is a monomer of a second heterologous oligomer assembly, namely bacteriophage T4 gp5 which has a cyclic point group of order 3. The second class of the protomer comprises a

first monomer, which is a monomer of a heterologous oligomer assembly, namely bacteriophage T4 gp27. The first monomer of the second protomer is fused to another monomer of a third oligomer assembly, namely human PTPS which belongs to a dihedral D3 point group of order 3. The Specification, therefore, provides an example of a protein lattice which can be established from a mixture of two different types of protomers. In addition to the examples of various protein lattices discussed above, the Specification teaches the structural and functional features common to the genus by providing the specific rotational symmetry alignment requirements for the quaternary structures of oligomer assemblies implemented in the fusion protein ("protomer") which would confer the self-assembling function of the protomer(s) into a protein lattice as discussed in the remarks of the Amendment previously filed on July, 21, 2008 (also see, the Specification at page 4, line 8 through page 8, line 3; page 10, line 4 through page 16, line 28; and Tables 1 and 2). The instant application provides specific teachings regarding the common structural features of the claimed invention along with their functions. Applicants' specification clearly evidences that Applicants had possession of the genus claims.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. First, claims are drawn to a genus of protein lattices having a regular structure with a repeating unit repeating in three dimensions, the repeating unit comprising protein protomer, wherein each protein protomer comprises at least a first monomer and a second monomer fused together, the monomers each being a monomer of an oligomer assembly into which the monomers

are assembled for assembly of the protomers into the lattice, and wherein said first monomer is a monomer of a first oligomer assembly which has at least three rotational symmetry axes; and wherein said second monomer is a monomer of a second oligomer assembly, said second oligomer assembly having a rotational symmetry axis of the same order as one of the at least three rotational symmetry axes of the first oligomer assembly and being aligned with the one of the at least three rotational symmetry axes of the first oligomer assembly when said protomers self-assemble into the lattice. Although Applicants argue that the specification describes some examples in Figures 1 and 2, it is noted by the Examiner that the disclosure of the specification is not read into the claims as a claim limitation, and those few examples provided in Figures 1 and 2, and proteins disclosed in Tables 1 and 2 fail to be representative species for the genus of any first and second monomers having essentially any structure.

Furthermore, in light of the fact that it is highly unpredictable for one of skill in the art to identify 3-D structure and rotational axes that may exist in any oligomer assemblies comprising any monomers, which includes proteins from their amino acid sequences, especially when two monomers that are fused together which may significantly alter the 3-D conformation of each of the two monomers, one of skill in the art would not have recognized that Applicants were in possession of the genus of protein lattices (see below 112 1st rejection under enablement for further discussion on “the unpredictability"). In support of the Examiner’s position, Applicants have stated that “at the time the instant application was filed, laboratory production of a protein lattice in accordance with the present invention had only been demonstrated for the quoted

example of human HFH and E. coli PurE" on page 13, last paragraph in the remarks filed on 07/23/2008. Taken together, the limited disclosure in the specification, i.e., a single protein lattice which can be made using human HFH and E. coli PurE, wherein said proteins have a specific rotational axes based on the octahedral point group and dihedral D4 point group, respectively, and the lack of any experimental data to support the notion that all possible combinations of any monomers having any set of rotational symmetry axes can be fused together to form a protein lattice, one of skill in the art would not have recognized that the genus of protein lattices, encompassing widely variant species having essentially any structure, can be used in extremely diverse applications as listed in pg. 25, i.e., catalyzing biotransformations, data storage, display, charge separation, nanowire, motor, mould and X-ray crystallography.

In addition, the claimed genus of protein lattices include those that are crystalline. Therefore, given [1] the high level of unpredictability associated with making a crystalline protein with an expectation that it is an X-ray diffraction-quality protein crystal, [2] the fact that a singular chemical composition can crystallize differently based on the crystallization conditions, [3] the space group and unit cell dimensions of a crystal of any given chemical composition can only be determined by analyzing that the crystal's X-ray diffraction data (Giege *et al*. Crystallogenesis of Biological Macromolecules: Facts and Perspectives. Acta Cryst., 1994, D50: 339-350), and [4] the lack of disclosure regarding how the genus of crystalline protein lattices can be used for an X-ray diffraction studies (see page 25 of the specification which lists "X-ray crystallography" as the intended use of the claimed invention), one of skill in the art

would not have recognized that Applicants were in possession of [A] the genus of protein lattices that are crystalline having any space group and any unit cell dimensions. In general, for the genus of crystalline protein lattices to be adequately described, the following must be disclosed: (1) the composition of the crystal (exact structural features of all molecules in the crystal must be described, i.e., the protein (preferably a SEQ ID NO of all included residues); (2) the space group; and (3) the unit cell dimensions of the crystal.

Given the lack of additional representative species of the genus of protein lattices having a regular structure with a repeating unit repeating in three dimensions, the repeating unit comprising protein protomer, wherein each protein protomer comprises at least a first monomer and a second monomer fused together, the monomers each being a monomer of an oligomer assembly into which the monomers are assembled for assembly of the protomers into the lattice, and wherein said first monomer is a monomer of a first oligomer assembly which has at least three rotational symmetry axes; and wherein said second monomer is a monomer of a second oligomer assembly, said second oligomer assembly having a rotational symmetry axis of the same order as one of the at least three rotational symmetry axes of the first oligomer assembly and being aligned with the one of the at least three rotational symmetry axes of the first oligomer assembly when said protomers self-assemble into the lattice, wherein the genus of any first and second monomers which can be assembled into a lattice encompasses widely variant crystalline and non-crystalline polypeptides and monomers essentially having any structure, Applicants have failed to sufficiently describe the

claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention. For the reasons provided herein and in the previous office action, the rejection under this statute is maintained.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1, 5 and 7-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, because the specification, while being enabling for a protein lattice comprising a fusion protein comprising the human ferritin heavy chain (HFH) and the E. coli PurE encoded by human HFH and E. coli PurE with the specific point group as shown in Figure 1, does not reasonably provide enablement for any crystalline or non-crystalline protein lattices having a regular structure with a repeating unit repeating in three dimensions, the repeating unit comprising protein protomer, wherein each protein protomer comprises at least a first monomer and a second monomer fused together, the monomers each being a monomer of an oligomer assembly into which the monomers are assembled for assembly of the protomers into the lattice, and wherein said first monomer is a monomer of a first oligomer assembly which has at least three rotational symmetry axes; and wherein said second monomer is a monomer of a second oligomer assembly, said second oligomer assembly having a rotational symmetry axis of the same order as one of the at least three rotational

symmetry axes of the first oligomer assembly and being aligned with the one of the at least three rotational symmetry axes of the first oligomer assembly when said protomers self-assemble into the lattice, wherein any first and second monomers which can be assembled into a lattice encompass widely variant crystalline and non-crystalline monomers including any proteins essentially having any structure. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The rejection was stated in the previous office action as it applied to previous claims 1, 5 and 7-25. In response to this rejection, Applicants have canceled Claims 2-4, 6, 28 and 34, and amended Claims 1, 5, 7, 8, 11-15, 18, 24, 25, 27, 29, 30, 31 and 33, and traverse the rejection as it applies to the newly amended claims.

Applicants' arguments are as follows:

The Breadth and Nature of the Claims

The claimed invention is directed to the genus of protein lattices having a regular structure with a repeating unit(s) of protein protomers. Each protein protomer comprises at least two monomers fused together and the monomers each being a monomer of an oligomer assembly. The first monomer is a monomer (a subunit of a oligomer protein complex) of an oligomer assembly (an oligomer protein complex referred in the present application as "first oligomer assembly"). The first oligomer assembly has at least three rotational symmetry axes. The first monomer is fused to a second monomer which is a monomer of another oligomer assembly ("second oligomer assembly" as amended). The second oligomer assembly, according to the invention, has a rotational symmetry axis of the same order as one of the set of rotational symmetry axes of the first oligomer assembly and the rotational symmetry axis of the second oligomer assembly is aligned with the one of the rotational symmetry axes of the first oligomer assembly when the protomers self-assemble into the lattice. The protein lattice of the present invention can be used, for example, as a support in X-ray crystallography (the Specification at page 24, line 7 through page 25, line 1).

The State of the Prior Art

Methodology involved in making fusion proteins (e.g., chimeric proteins) and providing suitable conditions for protomer assembly were routine at the time the invention was made. For example, the formation and production of the protomers are described in the Specification (the Specification at page 8, line 4 through page 10, line 3; at page 19, line 2 through page 21, lines 5- 8). The formation and production of fusion proteins are also well known in the art (e.g., WO 2000/68248, the entire teachings of which are incorporated by reference in the present application). One of ordinary skill in the art routinely created various types of fusion proteins by either recombinant technology or crosslinking technology at the time the invention was made. Suitable conditions for the protomer assembly processes for potential protomers were also well known and described in the art as taught in WO 2000/68248 (see the present Specification at page 21, lines 13-14).

The Level of One of Ordinary Skill in the Art

The level of one of ordinary skill in the art was the level of ordinary skill in structural biology and bioinformatics who are specialized in protein designs in an academic or industrial setting. The Amount of Direction Provided By the Inventors As stated above, an absolute certainty is not required for enablement. The requisite conditions for monomers and oligomer assembly in order for resultant protomers to form the claimed protein lattice are well described in the Specification. Specifically, the requisite rotational symmetries and alignment of oligomer assemblies of the claimed invention is well described in the Specification. The protein lattices of the present invention can be designed by selecting oligomer assemblies having appropriate symmetries (the Specification at page 4, lines 8-19). The principle by which symmetries of the lattices derive from the symmetry axes of the oligomers assemblies is also taught in detail in the Specification (the Specification at page 4, line 26 through page 8, line 3). Numerous examples of the combinations of symmetries of the oligomer assemblies which allow formation of the claimed protein lattices are also provided, for example, as enumerated in Tables 1 and 2 (the Specification at page 10, line 4 though page 16 line 28). Table 1 provides examples of homologous protomers capable of forming a protein lattice and Table 2 lists examples of heterologous protomers capable of forming a protein lattice. The Specification also teaches that information regarding possible oligomer assemblies and their rotational symmetry axes are generally available and well known in the art (the Specification at page 4, lines 13-19). Table 3 provides examples of oligomer assemblies which share a common point group as mentioned in Tables 1 and 2. Candidate monomers of the present invention, whose oligomer assemblies have the requisite symmetries and orders can be selected by referring to, for example, Tables 1, 2 and 3 of the Specification as well as information available in the art. According to the present invention, it is, therefore, the characteristics involving rotational symmetry axes of oligomer assembly and their orders that need to be identified, not the specific physical and chemical properties of a potential oligomer assembly or articulated fusion techniques. Accordingly, the present application provides sufficient guidance to make and use the present invention which is not limited to particular oligomer assemblies, but

extends to oligomer assemblies having a quaternary structure with the requisite rotational symmetry and order.

The Level of Predictability in the Art

Achieving the claimed invention, once one of ordinary skill in the art understand the primary principles involved in creating the claimed protein lattice as taught in great detail in the Specification, was predictable. Previously, Applicants submitted post-filing evidence of enablement, Exhibit A, which was filed at the European Patent Office on August 16, 2006 in connection with European Patent Application No. 03753741.2. The document provides an additional 3D regular protein lattice experimentally demonstrated in accordance with the present invention in addition to the protein lattices provided in Figures 1 and 2 of the Specification. This post-filing success demonstrates the claimed invention is highly enabling and can be achieved with a high level of predictability once one of ordinary skill in the art recognizes the underlying principles of the present invention.

The Existence of Working Examples

Figure 1 of the Specification depicts an example of a protein lattice established from assembly of homogeneous protomers represented by p4d4. The first oligomer assembly, as exemplified in Figure 1, is human ferritin heavy chain (HFH) which belongs to an octahedral point group of order 4 (P4). The second oligomer assembly is E. coli PurE which belongs to a dihedral point group of order 4 (d4). Figure 1 of the Specification, therefore, provides an example of a protein lattice which are established from homogenous protomers, whose oligomer assemblies have a point group of order 4 and are aligned with the one of the rotational symmetry axes of the first oligomer assembly when the protomers self-assemble into the lattice. In Figure 2, the Specification provides a more complex protein lattice formed from two mixed types of heterogeneous protomers, each represented by p3C3A and d3C3A, respectively. The first promoter of the protein lattice of Figure 2 comprises a first monomer of a first oligomer assembly, namely E. coli dps, which belongs to a tetrahedral point group of order 3. The first monomer of the first protomer in Figure 2 is then fused to a second monomer, which is a monomer of a second heterologous oligomer assembly, namely bacteriophage T4 gp5 having a cyclic point group of order 3. The second class of the protomer of Figure 2 comprises a first monomer which is the other monomer of the heterologous oligomer assembly of bacteriophage T4, namely T4 gp27 which belongs to a cyclic point group of order 3. The first monomer of the second protomer is, then, fused to another monomer of a third oligomer assembly, namely human PTPS which belongs to a dihedral D3 point group of order 3. Figure 2 of the Specification provides an example of a protein lattice which are established from a mixture of two hetergeneous protomers, whose oligomer assemblies have a point group of order 3 and are aligned with the one of the rotational symmetry axes of the first oligomer assembly when the protomers self-assemble into the lattice. In addition, as discussed above, Applicants submitted a post-filing evidence of enablement, Exhibit A, a copy of a document filed at the European Patent Office on August 16, 2006 in connection with

European Patent Application No. 03753741.2. The document describes an additional experimentally demonstrated 3D regular protein lattice in accordance with the present invention. A first oligomer assembly is a small heat shock protein (SHS) having P4 symmetry (octahedral or cubic symmetry) and the second oligomer assembly is the streptavidin/streptag assembly having d2 symmetry (dihedral symmetry of order 2).

The Quantity of Experimentation Needed to Make or Use the Invention Based on the Content of the Disclosure

It would only take routine experimentation, not undue experimentation, for one of ordinary skill in the art to make and use the claimed invention using the disclosure of Applicants' specification. Ample guidance on the principle involved in making and using the invention is provided and the working examples are presented in detail in the Specification as discussed above. Further, Tables 1-3 provide various types of protomers having specific rotational symmetries with specific orders suitable for forming a stable structure of the protein lattices of the claimed invention. Since the level of ordinary skill in the art was such that it would be routine experimentation to make and use the claimed protein lattices once the requisite elements for protomers suitable for forming claimed protein lattices are recognized as taught by the Specification, one of ordinary skill in the art would not have to engage in undue experimentation to make and use the claimed invention. Applicants further argue that they are not required to teach in detail all experimental procedures for every possible protein protomer encompassed by the present claims. The ways in which appropriate oligomer assemblies are selected and methods for fusing two monomers of the chosen oligomer assemblies are well described in the Specification (see the Specification at page 8, line 25 through page 10, lines 3; page 19, lines 18-27) and was also known in the art at the time of the invention (see WO 2002/68248). Further, as discussed above, the Specification provides ample guidance on the principles for establishing the claimed protein lattices from protomers which enable the formation of such protein lattices. Therefore, given the level of one of ordinary skill in the art and predictability and it would not take undue experimentation for one of ordinary skill in the art to make and use the claimed invention based on the teachings of the Specification and what was known in the art.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. First, the scope of the claims encompasses any crystalline or non-crystalline protein lattices having a regular structure with a repeating unit repeating in three dimensions, the repeating unit comprising protein protomer, wherein each protein protomer comprises at least a first monomer and a second monomer fused together, the monomers each being a monomer of an oligomer

assembly into which the monomers are assembled for assembly of the protomers into the lattice, and wherein said first monomer is a monomer of a first oligomer assembly which has at least three rotational symmetry axes; and wherein said second monomer is a monomer of a second oligomer assembly, said second oligomer assembly having a rotational symmetry axis of the same order as one of the at least three rotational symmetry axes of the first oligomer assembly and being aligned with the one of the at least three rotational symmetry axes of the first oligomer assembly when said protomers self-assemble into the lattice, wherein any first and second monomers which can be assembled into a lattice encompass widely variant crystalline and non-crystalline monomers including any proteins essentially having any structure. However, the specification lacks disclosure of how any protein lattices comprising any first and second monomers that are fused together essentially having any structure correlate with a desired function/activity, i.e., those monomers each being a monomer of an oligomer assembly into which the monomers are assembled for assembly of the protomers into the lattice, and wherein said first monomer is a monomer of a first oligomer assembly which has at least three rotational symmetry axes; and wherein said second monomer is a monomer of a second oligomer assembly, said second oligomer assembly having a rotational symmetry axis of the same order as one of the at least three rotational symmetry axes of the first oligomer assembly and being aligned with the one of the at least three rotational symmetry axes of the first oligomer assembly when said protomers self-assemble into the lattice, or those protein lattices that can be made into crystalline forms for use in the X-ray crystallography (see page 25 of the

specification which lists "X-ray crystallography" as the intended use of the claimed invention).

It is noted that the state of the art at the time of the invention acknowledges a high level of unpredictability for [1] making a protein crystal, i.e., a protein lattice, with an expectation that it is X-ray diffraction-quality or [2] predicting the number of rotational symmetry axis of a protein from its amino acid sequences. Branden et al. ("Introduction to Protein Structure Second Edition", Garland Publishing Inc., New York, 1999) teaches that "[c]rystallization is usually quite difficult to achieve" (p. 375) and that "[w]ell-ordered crystals…are difficult to grow because globular protein molecules are large, spherical, or ellipsoidal objects with irregular surfaces, and it is impossible to pack them into a crystal without forming large holes or channels between the individual molecules" (p. 374). Also, Drenth ("Principles of X-ray Crystallography," Springer, New York, 1995) teaches that "[t]he science of protein crystallization is an underdeveloped area" and "[p]rotein crystallization is mainly a trial-and-error procedure" (p. 1). One cannot predict *a priori* those conditions that will lead to the successful crystallization of a diffraction-quality crystal nor can one predict the space group symmetry or unit cell dimensions of the resulting crystal. See Kierzek et al. (*Biophys Chem* 91:1-20, 2001), which teaches that "each protein crystallizes under a unique set of conditions that cannot be predicted from easily measurable physico-chemical properties" and that "crystallization conditions must be empirically established for each protein to be crystallized" (underline added for emphasis, p. 2, left column, top). Thus, in view of these teachings, a skilled artisan would recognize that it is highly unpredictable as to make and use the scope of the

invention as claimed, and it would require undue experimentation to determine which structure, out of infinite number of possible protein lattices that are crystalline can be used for X-ray crystallography. As such, given the limited disclosure provided by the specification, i.e., human HFH and E. coli PurE which can be fused together to form a protein lattice, wherein said proteins have a specific rotational axes based on the octahedral point group and dihedral D4 point group, respectively, the scope of the claimed invention is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of crystalline or non-crystalline protein lattices comprising any first and second monomers having essentially any structure.

Even if one argues that the present invention differs from a typical protein invention in that it is not concerned directly with the chemical and biochemical properties of the protein as such, but rather, concerned with a principle based on the symmetry of the quaternary structure of the proteins, in light of the fact that [1] it is highly unpredictable for one of skill in the art to identify 3-D structure and rotational axes that may exist in a protein from its amino acid sequence, especially when two proteins that are fused together which may significantly alter the 3-D conformation of each of the two proteins, [2] the specification lacks of any guidance and experimental data with respect to how all possible combinations of all monomers/proteins, optionally having at least three rotational symmetry axes can be fused together to form a protein lattice, and [3] Applicants' admission that "at the time the instant application was filed, laboratory production of a protein lattice in accordance with the present invention had only been demonstrated for the quoted example of human HFH and E. coli PurE" (see on page 13,

last paragraph in the remarks filed on 07/23/2008), it would require one of skill in the art undue experimentation to make and use the claimed invention.

Taken together, although the method of making fusion proteins was known in the art at the time the instant application was filed, it would require undue experimentation for one of skill in the art to test any crystalline or non-crystalline protein lattices having a regular structure with a repeating unit repeating in three dimensions, the repeating unit comprising protein protomer, wherein each protein protomer comprises any first monomer and any second monomer fused together, the monomers each being a monomer of an oligomer assembly into which the monomers are assembled for assembly of the protomers into the lattice, and wherein said first monomer is a monomer of a first oligomer assembly which has at least three rotational symmetry axes; and wherein said second monomer is a monomer of a second oligomer assembly, said second oligomer assembly having a rotational symmetry axis of the same order as one of the at least three rotational symmetry axes of the first oligomer assembly and being aligned with the one of the at least three rotational symmetry axes of the first oligomer assembly when said protomers self-assemble into the lattice, wherein any first and second monomers which can be assembled into a lattice encompass widely variant crystalline and non-crystalline monomers including any proteins essentially having any structure, optionally having any symmetry, space group, and unit cell dimensions, out of an infinite number of possible combinations, and identify those that can be used in applications as intended by Applicants, i.e., catalyzing biotransformations, data storage, display, charge separation, nanowire, motor, mould and X-ray crystallography (see pg.

25). For the reasons provided herein and in the previous office action, the rejection under this statute is maintained.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of any protein lattice having the desired biological characteristics/functions is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The previous rejection of Claims 1, 5 and 7-25 under 35 U.S.C. § 102(b) as being anticipated by Padilla et al. (Nanohedra: Using symmetry to design self assembling protein cages, layers, crystals, and filaments, PNAS, 2001, Vol. 98, No. 5, pg. 2217–2221, see IDS), in view of the evidentiary reference Hestenes (Retrieved from the Internet at <http://modelingnts.la.asu.edu/pdf/crystalsymmetry.pdf>, [Retrieved on

3/18/08]), is withdrawn because Padilla et al. do not teach a protein lattice with "at least three rotational symmetry axes".

Claims 1, 5, 7-23 and 25 are rejected under 35 U.S.C. § 102(b) as being anticipated by Dotan et al. (Self-Assembly of a Tetrahedral Lectin into Predesigned Diamondlike Protein Crystals, Angew. Chem. Int. Ed. 1999, 38, No. 16, pp: 2363-2366).

The instant claims are drawn to a protein lattice having a regular structure with a repeating unit repeating in three dimensions, the repeating unit comprising protein protomer, wherein each protein protomer comprises at least a first monomer and a second monomer fused together, the monomers each being a monomer of an oligomer assembly into which the monomers are assembled for assembly of the protomers into the lattice, and wherein said first monomer is a monomer of a first oligomer assembly which has at least three rotational symmetry axes; and wherein said second monomer is a monomer of a second oligomer assembly, said second oligomer assembly having a rotational symmetry axis of the same order as one of the at least three rotational symmetry axes of the first oligomer assembly and being aligned with the one of the at least three rotational symmetry axes of the first oligomer assembly when said protomers self-assemble into the lattice.

Dotan et al. teach a three-dimensional protein lattice having a regular structure with a repeating unit repeating in three dimensions, the repeating unit comprising protein protomer, i.e., tetrameric tetrahedral lectin concanavalin A, wherein each protein protomer comprises at least a first monomer, i.e., a monomeric lectin concanavalin A-1

("-1" denotes that it is the 1 of 4 tetrameric tetrahedral lectin concanavalin A-1), and a second monomer, i.e., a monomeric lectin concanavalin A-2 ("-2" denotes that it is the 2 of 4 tetrameric tetrahedral lectin concanavalin A-1), fused together, the monomers each being a monomer of an oligomer assembly into which the monomers are assembled for assembly of the protomers into the lattice, and wherein said first monomer is a monomer of a first oligomer assembly, i.e., first tetrameric tetrahedral lectin concanavalin A, which has at least three rotational symmetry axes; and wherein said second monomer is a monomer of a second oligomer assembly, i.e., second tetrameric tetrahedral lectin concanavalin A unit, said second oligomer assembly having a rotational symmetry axis of the same order as one of the at least three rotational symmetry axes of the first oligomer assembly and being aligned with the one of the at least three rotational symmetry axes of the first oligomer assembly when said protomers self-assemble into the lattice (see page 2364 and Figure 1), which anticipates claims 1, 5, 9-21 (see the claim interpretation of claims 16-18 and 20 under 112 2nd paragraph rejections above). Claims 7 and 8 are included in this rejection because Dotan et al. teach a linker, i.e., bismannopyranoside 2 (see page 2364, right column for the structure of the bismannopyranoside 2), which is used to fuse said monomeric lectin concanavalin A in to a tetrameric form (see the claim interpretation of claim 8 under 112 2nd paragraph rejections above). Claim 22 is included because hundreds if not thousands of “other" tetrameric tetrahedral lectin concanavalin As as shown in Figure 4 of Dotan et al. meet the limitation of “an array of macromolecular entities attached thereto". Claim 23 is included in this rejection because the bismannopyranoside 2

taught by Dotan et al. acts as "an affinity tag" for monomeric tetrahedral lectin concanavalin As since each of the monomeric tetrahedral lectin concanavalin As has 4 specific binding sites for the mannopyranoside (see the paragraph below Figure 1 on page 2364). Therefore, teachings of Dotan et al. anticipate claims 1, 5, 7-23 and 25.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 5 and 7-25 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-31 and 33 of copending Application No. 11/807922.

The rejection was stated in the previous office action as it applied to previous claims 1, 5 and 7-25. In response to this rejection, Applicants have canceled Claims 2-

4, 6, 28 and 34, and amended Claims 1, 5, 7, 8, 11-15, 18, 24, 25, 27, 29, 30, 31 and 33, and do not traverse the rejection as it applies to the newly amended claims. Applicants note that upon allowance, Applicants will address any double patenting rejections in the remarks filed on 07/23/2008. For Applicants' convenience the previous rejection is reiterated below with a minor change to account for the amendment to claims.

Claims 1, 5 and 7-25 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-31 and 33 of copending Application No. 11/807922. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to a protein lattice comprising repeating units of protein protomers comprising at least first and second monomers fused together, and further having at least three rotational symmetry axis, thereby having overlapping scope of the claimed invention. Further more, claims are supported by almost identical specifications.

A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. § 3.73(b).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Claims 1, 5, and 7-25 are rejected for the reasons as stated above. Applicants must respond to the objections/rejections in this Office action to be fully responsive in prosecution.

This office action is non-final.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jae W. Lee whose telephone number is 571-272-9949. The examiner can normally be reached on 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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